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Role of serum melatonin level in COVID-19 mortality and hospital admission

Yasemin Yılmaz Aydın[1] Aynur Yurtseven[1] Kerem Ensarioğlu[2] Kemal Aydın[1]
Cemil Kavalcı[3] Emine Bahar Kurt[4] Fatma Uçar[5]

[1]Department of Emergency Medicine, Dışkapı Yıldırım Beyazıt Training and Research Hospital, University of Health Sciences, Ankara, Turkey
[2]Department of Pulmonary Medicine, Ankara Atatürk Sanatoryum Training and Research Hospital, University of Health Sciences, Ankara, Turkey
[3]Department of Emergency Medicine, Antalya Training and Research Hospital, University of Health Sciences, Antalya, Turkey
[4]Department of Pulmonary Medicine, Ankara Etlik State Hospital, Ankara, Turkey
[5]Department of Biochemistry, Faculty of Health Sciences Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey

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Corresponding Author: Kerem Ensarioğlu, kerem.ensarioglu@gmail.com

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ABSTRACT

Aims: Coronavirus disease 2019 (COVID-19) is a zoonotic virus that presents itself with a broad spectrum of respiratory involvement. Without any specific treatment, various treatment modalities and markers for severity have been suggested. This study aimed to investigate the role of melatonin in the severity of COVID-19 infection, with the hypothesis that melatonin levels correlated with mortality, ward and intensive care unit (ICU) admission.

Methods: The study was performed as a single-center prospective cohort. Patients evaluated at the emergency ward for COVID-19 suspicion were defined as the study population. Those who had at least one COVID-19 RT-PCR positivity and did not have a history of cranial operation, being a shift worker, or under melatonin treatment were chosen. Ninety-six patients who had all the criteria fulfilled were deemed suitable for the study. Descriptive analysis for demographic data, Spearman correlation, and Mann-Whitney test for nonparametric evaluation were used.

Results: Eighty patients were considered suitable after excluding 16 patients, primarily due to improper melatonin sampling times. A positive correlation was seen between melatonin levels and intensive care admission, which was not observed in ward admission or overall mortality. This implicates the possibility of melatonin being used as a marker for the severity analysis of COVID-19.

Conclusion: With limited sensitivity, melatonin may be used to evaluate ICU admission. Its role regarding ward admission and overall mortality remains limited.

Keywords: Critical care, COVID-19, melatonin, mortality

INTRODUCTION

Corona viruses (COV) are an RNA virus, which is zootonic in nature. They often present in humans with respiratory involvement, varying from mild upper respiratory symptoms to acute respiratory distress syndrome. Coronavirus Disease 2019 (COVID-19), aptly named for its emergence in 2019 at Wuhan, China; represents the extreme end of its spectrum, with high virulence and mortality. With no specific treatment in sight, vaccination studies appear to be the only viable approach to disease control.[1]

Various suggestions and treatment modalities have been discussed for reducing the severity of COVID-19 infection. Melatonin is a topic of discussion with a potential role in inflammatory syndromes and sepsis.[2-6] It is expected to act as a limiting factor in the cytokine storm of COVID-19 by its antioxidant and anti-inflammatory effects. Reduction in melatonin levels in the elderly can also contribute to the severity of the disease in this age group. In experimental models, melatonin was proven protective against inflammatory and oxidative stress.[5] Studies have also shown the antiviral properties of melatonin against other viruses.[6-7] The role of melatonin in COVID-19 infection remains an issue of discussion, as currently available data can only allow assumptions.

The goal of the study was to investigate the role of melatonin in COVID-19 infection. The study hypothesized that decreased melatonin levels would increase overall mortality and contribute to hospital admission requirements.

METHODS

The study was performed as a single-center cohort study after approval from the Ethical Committe of Dışkapı Training and Research Hospital (Date: 17.05.2021, Decision No: 111/02). It was planned and prepared according to the Guidelines

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for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). The enlistment period of the study was between June 1st and December 1st; however, earlier cessation of the period was to be considered if an adequate number of patients were accepted. An estimated duration was assumed to be two months, which included one month of follow-up. This assumption was made after investigating the number of COVID-19 patients applied to the emergency ward in the last three months. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients older than 18 years old and with at least one confirmed positive COVID-19 reverse transcription polymerase chain reaction (RT-PCR) were considered eligible for the study. Exclusion criteria were patients' refusal to participate, being under melatonin treatment for any reason, being a shift worker, and having a history of any cranial operation. Informed consent was received from the patients, both written and verbal. The additional blood sample required for the study was planned to be taken alongside the routine requested blood samples. The routine samples consisted of a standardized COVID-19 panel, which included complete blood count, liver and renal function tests, inflammatory markers from serum, and arterial blood sampling for the evaluation of desaturation and lactate.

For standardization purposes, blood samples for melatonin levels were only received from samples provided between 08:00 AM and 10:00 AM. The blood samples were then transported in a standard vacutainer blood collection tube within 30 minutes to be centrifuged at a 1000 rate per minute for fifteen minutes. These samples were stored at -70°C and later transported to the laboratory of biochemistry department for enzyme-linked immuno-sorbent assay (ELISA) testing.

Regarding follow-up methodology, patients admitted to either the COVID-19 ward or intensive care units (ICU) were evaluated for mortality. This evaluation period was up to one month, starting from the initial diagnosis. Patients who were deemed suitable for outpatient follow-up were also subject to the exact duration of follow-up. Survival data of the patients' was to be received from the national database, which reports if the patient is alive whenever the records are accessed. This database was used for this purpose and not for additional data.

Mortality was accepted as the primary outcome of this study. Hospitalization requirement for the ward and/or ICU was the secondary outcome, with the ICU admission reflecting a worse prognosis. Vital signs, comorbidities, age, gender, and elevated white blood cell count were accepted as independent parameters due to their role in pneumonia scoring systems. Lactate levels were also accepted as another independent parameter, with computed thoracic tomography findings accepted as confounding parameters, as these findings mainly were used to evaluate how many lobes were involved rather than a separate parameter itself.

CURB-65 and pneumonia severity index (PSI) were the predictors for which the overall mortality comparison would be made to verify any possible correlation. Quick Sequential Organ Failure Assessment (qSOFA) scoring was used to predict ICU admission. Melatonin level was the primary diagnostic criterion hypothesized to affect mortality and hospital admission. CURB-65, PSI and qSOFA were also the main factors utilized in emergency service for requirement of ICU admission.

The hospital computer system, emergency ward records, and the study's patient chart, which included the data mentioned above, were utilized as data sources, the hospital computer system, emergency ward records, and the study's patient chart. The study patient follow-up chart consisted of a single form in Microsoft Word format. This form allowed a quick overview of the patient and was the primary data source for statistical analysis. The hospital computer system and hand-written records were referred for validation if data was missing from this form.

Selection bias was presumed due to the nature of the study. It was addressed as, besides the evaluation of melatonin level, no difference in treatment or presence of additional exposure was present. An average of 100 patients was expected to be enlisted and followed in this prospective study. Estimated loss during patient enlistment was assumed to be around 10% due to blood sampling techniques, logistics of transportation, and rapid deterioration, which would prevent an optimal evaluation. Assuming a mean melatonin level of 10(±5) ng/ml among healthy populations from epidemiologic studies, to validate an increase or decrease of 20%, 49 patients were deemed the minimal amount for a power of 80% and type-1 error of 0.05.[8]

Vital signs and blood sample results consisted of quantitative variables. Subgrouping was then performed to placate these variables as qualitative variables for their role in pneumonia scoring systems.

Descriptive statistics were used for demographic data, with the results being reported with case counts (n), median, and percentile distribution when appropriate. Kolmogorov-Smirnov was used for normality analysis. Spearman correlation and Mann-Whitney test were utilized to correlate two nonparametric results, depending on the parameter's type. No subgroups were defined for this study.

In case of missing data for any data regarding patients, removal from the study was planned. It was the choice as neither mean imputation nor available case validation would have been sufficient, given the combination of nominal and scale variables. To illustrate, the absence of a vital sign would also affect pneumonia scoring systems and further complicate the analysis, thus necessitating the removal of the patient if any data was missing. Due to the study's design, no loss to follow-up was expected. International Business Machines (IBM) Statistical Product and Service Solutions (SPSS) Edition 23 was the choice of statistical program in this study.

RESULTS

Patients were considered as candidates after the initial emergency ward evaluation. A total of 846 patients were evaluated at the COVID-19 emergency service isolation ward. Four percent (n=36) of patients had repeated admission; thus, the unique admission number was reduced to 816. Nearly half of the group was excluded from the study (n=458, 56%), as they either did not have a COVID-19 RT-PCR result, had a former positivity that could not be confirmed, did not stay in the ward long enough for a test result or were diagnosed by imaging modalities. The remaining 358 patients were eligible for the study. Most of the patients (n=362, 79% of the eligible group) refused to participate in the study or were not in a state to be informed about the study directly.

Ninety-six patients who had agreed to participate verbally and in writing were then accepted to the study as the final

group. However, 14 patients (14%) were removed, despite being initially suitable, due to either differences in blood sampling techniques or inadequate transportation. An additional patient was removed due to exitus before being admitted to any ward, and one patient was removed due to severe sepsis, which affected the blood sampling methodology (Figure 1).

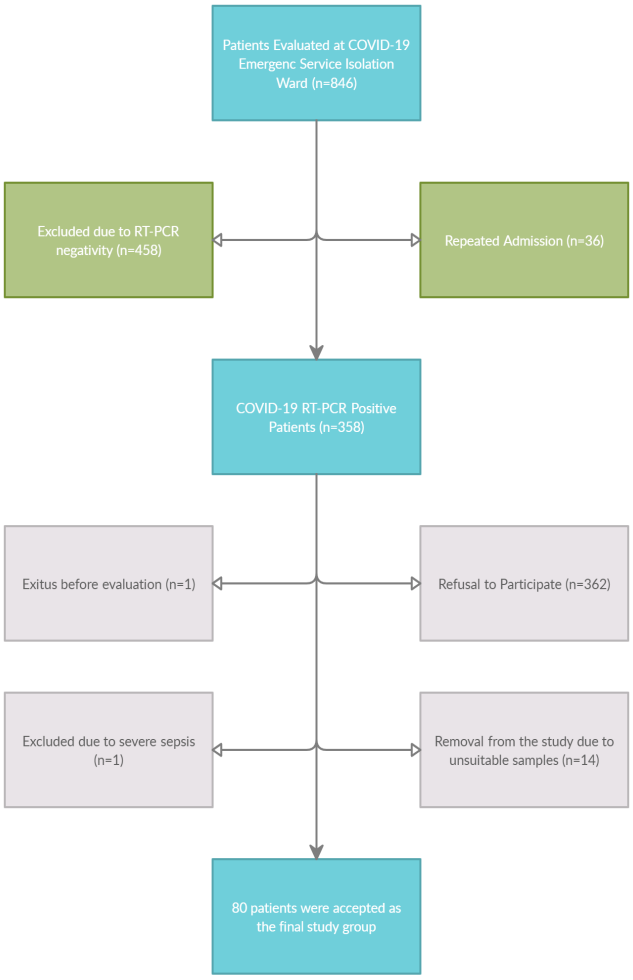
Patients Evaluated at COVID-19 Emergenc Service Isolation Ward (n=846)
Excluded due to RT-PCR negativity (n=458)
Repeated Admission (n=36)
COVID-19 RT-PCR Positive Patients (n=358)
Exitus before evaluation (n=1)
Refusal to Participate (n=362)
Excluded due to severe sepsis (n=1)
Removal from the study due to unsuitable samples (n=14)
80 patients were accepted as the final study group

Figure 1. Patient evaluation flow chart

The demographic evaluation showed that 43 (53,8%) patients were male and 37 (46,3%) females, with an average age of 64. Thirty-seven (46,3%) were vaccinated twice; those who had at least one vaccination for COVID-19 comprised half of the patients (n=40). All vaccination types available in the country regardless of subtype were accepted as a positive vaccination history, with two vaccination history being deemed adequate for vaccination. Fifteen patients (18,8%) had impaired mental condition, and 64 (80%) had computer tomography findings consistent with COVID-19 pneumonia.

The most commonly observed comorbidities were diabetes mellitus, hypertension, and coronary artery disease. (n=19, 15 and 6, respectively). Twenty-one patients had no known disease, with 19 having at least one and 12 having two known diseases. Thirty-nine (48.7%) were retired at the time of admission, 22 (27.5%) were unemployed, and the remaining 19 (%23.7) patients were non-shift workers (Table 1).

Regarding hospitalization, two patients were discharged from the emergency service, while 52 (65%) required admission to the COVID-19 ward. The remaining 26 (n=32,5%) had to be followed up under intensive-care conditions. Ten patients (12.5%) had at least one complication during treatment. Seventeen patients (21.3%) were lost in overall mortality within the one-month follow-up period (Table 2).

Table 1. Demographic Information

Parametres		Number	Percentage (%)
Gender	Male	43	53.8
	Female	37	46.3
	Total	80	100
Age	Average	63	
	SD	14	
	Total	80	
Mental Status	Normal	65	81.3
	Abnormal	15	18.8
	Total	80	100
Vaccination History	None	40	50
	1 Dosage	3	3.8
	2 Dosage	37	46.3
	Total	80	100
COVID-19 CT Findings	Present	64	80
	Absent	16	20
	Total	80	100
Comorbidities	DM	19	23
	HT	15	18
	CAD	6	7
Occupational Status	Retired	39	48.7
	Unemployed	22	27.5
	Non-shift Worker	19	23.7
	Total	80	100

SD: Standart deviation, **CT**: Computed tomography, **DM**: Diabetes mellitus, **HT:** Hypertension, **CAD**: Coronary artery disease

Table 2. Hospitalization, complications and mortality

Parametres		Number	Percentage (%)
Treatment localization	Outpatient	2	2.5
	Ward	52	65
	Intensive care	26	32.5
	Total	80	100
Progression	Complication	10	12.5
	Mortality	17	21.3

Complication definition: Complications mentioned here include three cases of cerebrovascular events and one case of the following disease; acute kidney injure, delirium, liver injury, decompensated heart failure, myocardial infarctus and peptic ulcer perforation

A positive correlation was seen between melatonin levels and ICU admission. (p=0.005) This correlation was validated by the evaluation of other parameters which were related to ICU admission. Desaturation, respiratory rate, elevated WBC, lactate levels, and increased CURB-65, qSOFA, and PSI scores were found statistically significant in the same analysis. No correlation was found between melatonin levels and mortality, which again was verified by the scoring systems (Table 3).

In the Receiver Operating characteristic (ROC) analysis, a correlation between melatonin levels and ICU admission was demonstrated. (p=0.005, and area under curve=0.696) As melatonin levels increased, a lower admission to the ICU was observed (Figure 2).

Table 3. Mortality and hospital admission analysis

Parametres			Mortality	Ward Admission	ICU Admission
Spearman correlation between parametres	**Melatonin**	Correlation coefficient	-0.150	**.296****	**-.318****
		Sig. (2-tailed)	0.186	0.008	0.004
	Lactate	Correlation coefficient	0.213	-0.197	**.238***
		Sig. (2-tailed)	0.058	0.081	0.034
	WBC	Correlation coefficient	0.158	**-.357****	**.331****
		Sig. (2-tailed)	0.161	0.001	0.003
	CURB65	Correlation coefficient	.267*	**-.280***	**.258***
		Sig. (2-tailed)	0.017	0.012	0.021
	PSI	Correlation coefficient	.271*	**-.357****	**.341****
		Sig. (2-tailed)	0.015	0.001	0.002
	qSOFA	Correlation coefficient	0.203	**-.453****	**.479****
		Sig. (2-tailed)	0.072	0.000	0.000

*: Correlation is significant at the 0.05 level (2-tailed), **: Correlation is significant at the 0.01 level (2-tailed), **WBC**: White blood cell, **PSI**: Pneumonia severity index, **qSOFA**: Quick sequential organ failure assessment, **ICU**: Intensive care unit

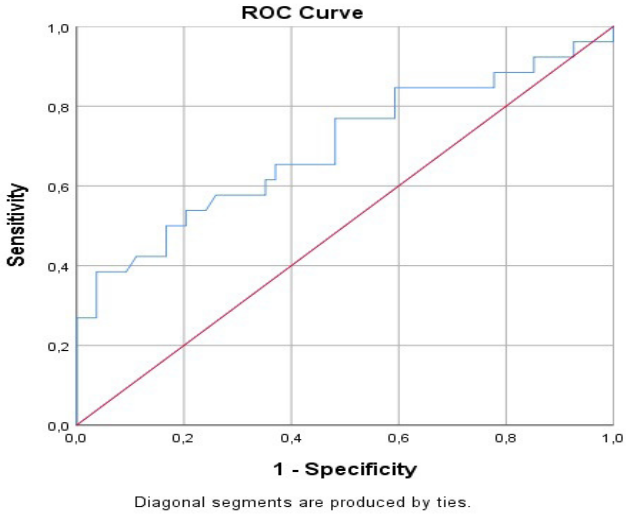

Figure 2. ROC curve of melatonin and intensive care admission

DISCUSSION

Melatonin levels were found relevant in ICU admission, while no statistical correlation was observed in overall mortality. These results show that the study's hypothesis was only partially correct, being limited to pointing out the localization of treatment rather than its prognosis. The melatonin levels also vary differently, and only at a high threshold does it predict ICU admission. This need for a high level of melatonin requirement might explain why supplemental melatonin intake was found effective in some studies rather than an increased basal level already present in the patients.[7,9] A randomized controlled study is underway by Garcia et al.[10] to investigate melatonin's role in symptomatic and asymptomatic patients. A similar trial has been prepared for patients in the ICU for the role of melatonin in the improvement of clinical parameters.[11]

While no reports have been presented as of this manuscript that supports melatonin's role in mortality reduction of COVID-19 infection, its role in lowering inflammatory markers has been reported at a dosage of 5-25 mg/day.[7,12] This dosage appears to be higher than the previously mentioned randomized controlled study's dosage plan. In summary, it can be concluded that while the elevation of melatonin levels may have a protective effect, the exact cut-off is yet to be proven in the currently available literature. Admitting melatonin to a particular group or as a general prophylaxis to the whole population without screening is another topic to be debated.

The study's main limitation was the limited population size caused by reduced COVID-19 levels in the surrounding area of the single-center hospital. This limitation was further worsened by the refusal of participation in most patients. This refusal was mainly attributed to the patients' and their families' stance against medical studies, which occurred in a similar prospective study of ours with up to 90% refusal of participation. We tried to avoid selection bias by preventing direct interaction between the study group's doctors and those who had offered the study. In a similar approach, all patients and/or their families who had applied to the COVID-19 emergency ward were offered to participate in the study. By this, we had hoped to prevent the selection of "stable" patients among the general population.

Another limitation of the study was a lack of a control group (patients suitable for outpatient follow-up) and a lack of repeated melatonin sampling for the patients. The control group exclusion was mainly due to different evaluation and routine inspection methods for outpatient follow-up, as these patients are not often required for an equally detailed routine laboratory work-up and imaging. Follow-up melatonin sampling could have provided additional information but was not planned as initial melatonin testing was utilized during COVID-19 routine evaluation, and repeated testing could not be put on a schedule for patients with varying follow-up periods.

Melatonin may be used as a marker for COVID-19 severity, albeit with limited sensitivity. Its role in mortality remains insignificant, while being statistically relevant in evaluating ICU admission may prove helpful. Combining melatonin with other markers or limiting its usage to a specific age group may be considered an option for better sensitivity and specificity. Further studies, especially those with higher recruitment rates and longer follow-up duration, are required to discuss the generalizability of melatonin as a marker for hospital admission evaluation. Additional studies, such as those already underway, would also allow a better dosage schedule if melatonin is considered as a prophylaxis method.

ETHICAL DECLARATION

Ethics Committee Approval: The study was carried out with the permission of Ethical Committe of Dışkapı Training and Research Hospital (Date: 17.05.2021, Decision No: 111/02).

Informed Consent: All patients signed and free and informed consent form.

Reviewer Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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